



Chance and risk of controlling rabies in large-scale and long-term immunized fox populations

L. Tischendorf¹, H.-H. Thulke¹, C. Staubach², M. S. Müller¹, F. Jeltsch¹, J. Goretzki³, T. Selhorst², T. Müller², H. Schlüter² and C. Wissel¹

¹Department of Ecological Modelling, Centre for Environmental Research Ltd, PO Box 2, 04301 Leipzig, Germany (luti@oesa.ufz.de)

²Federal Research Centre for Virus Diseases of Animals, Seestr. 15, 16868 Wusterhausen (Dosse), Germany (staubach@wus.bfav.de)

³Federal Research Centre for Forestry and Forest Products, 16201 Eberswalde, Germany

The large-scale immunization of European fox populations against rabies is currently under the microscope for reducing the considerable expenditure without putting public health at risk. Empirical knowledge is inadequate to interpret the lasting sporadic incidences and, therefore, to verify the final success of the immunization campaigns. By using a proven simulation model we show that rabies can persist on a very low level in the form of spatio-temporal moving infection clusters within a highly immunized fox population. We found further: (i) the existence of a threshold after which the chance of eradicating the disease by vaccination increases clearly, and (ii) that at least six years of 70% mean immunization rate are required to guarantee a likely success.

Keywords: red fox; rabies; epidemiology; immunization; disease pattern; simulation

1. INTRODUCTION

Rabies is one of the most hazardous zoonoses in the world. In global terms up to 50 000 people are estimated to die from rabies every year (Rupprecht *et al.* 1994; Meslin 1997). In Europe rabies occurs mainly in a sylvatic cycle. Nonetheless it causes numerous human infections (108 human cases were reported between 1977 and 1990 (WHO 1990a)) and economic problems (Curk 1991). For approximately 20 years, considerable efforts have been undertaken to control the current epidemic using oral immunization of the main wildlife reservoir, the red fox (*Vulpes vulpes*) (Stöhr & Meslin 1996). The WHO estimates that based on modern disease control policy, rabies can be eradicated in Europe by the end of this century (WHO 1990b).

Eastern Germany represents one of the largest coherent vaccination areas ever treated in Europe (compare Stöhr & Meslin (1996) and Masson *et al.* (1996)). About 108 000 km² have now been vaccinated for at least five years, with aircraft being used to distribute *ca.* 18–20 vaccine-filled baits per km² in spring and autumn. This extensive strategy enables *ca.* 70% of the fox population to be continuously immunized, resulting in a drastic decrease of rabies incidence (Stöhr *et al.* 1994; Schlüter & Müller 1995; see figure 1).

Although much effort has been undertaken to reduce the substantial hazard posed to health and the environment, some sort of proof of the final success is required, not only to justify the considerable expenditure, but also to rule out the risk of a new outbreak (Stöhr & Meslin

1996). However, the final success remains uncertain despite the well-organized surveillance programme deployed in eastern Germany (89 721 foxes have been registered during the past six years, 2013 of them were rabid, see also figure 1). This uncertainty results from the unknown host population size, the flat-case detection rate, which is estimated to range between just 2% (Braunschweig 1980) and 10% (Bacon & MacDonald 1981; Schlüter & Müller 1995), and the low probability of detection of infected foxes at the end of an epidemic (Bacon 1981). Even though some regions in eastern Germany are presumably free of rabies in view of its complete regional cessation, other subareas show lasting sporadic incidences. In spite of the uncertainty of low-level persistence of rabies, the termination or at least cut back of the expensive vaccination programme is currently under discussion (Selhorst & Schlüter 1997). However, a reduced vaccination programme leaves a serious risk of a remaining persistence of the disease, which in turn could trigger a new outbreak. In addition, the increased density of foxes (Steck & Wandeler 1980; Goretzki & Paustian 1982; Voigt *et al.* 1985) would provide the basis for a new epidemic and cause a spread of the disease as dramatic or even worse as if vaccination had never been done (Schenzle 1995). For these reasons the termination of vaccination requires answers to the following questions. What is the overall risk of the potential low-level persistence of rabies in immunized fox populations, not only for one region but also for diverse biological and epidemiological settings? What are the ranges of the two main controlling variables, immunization rate and

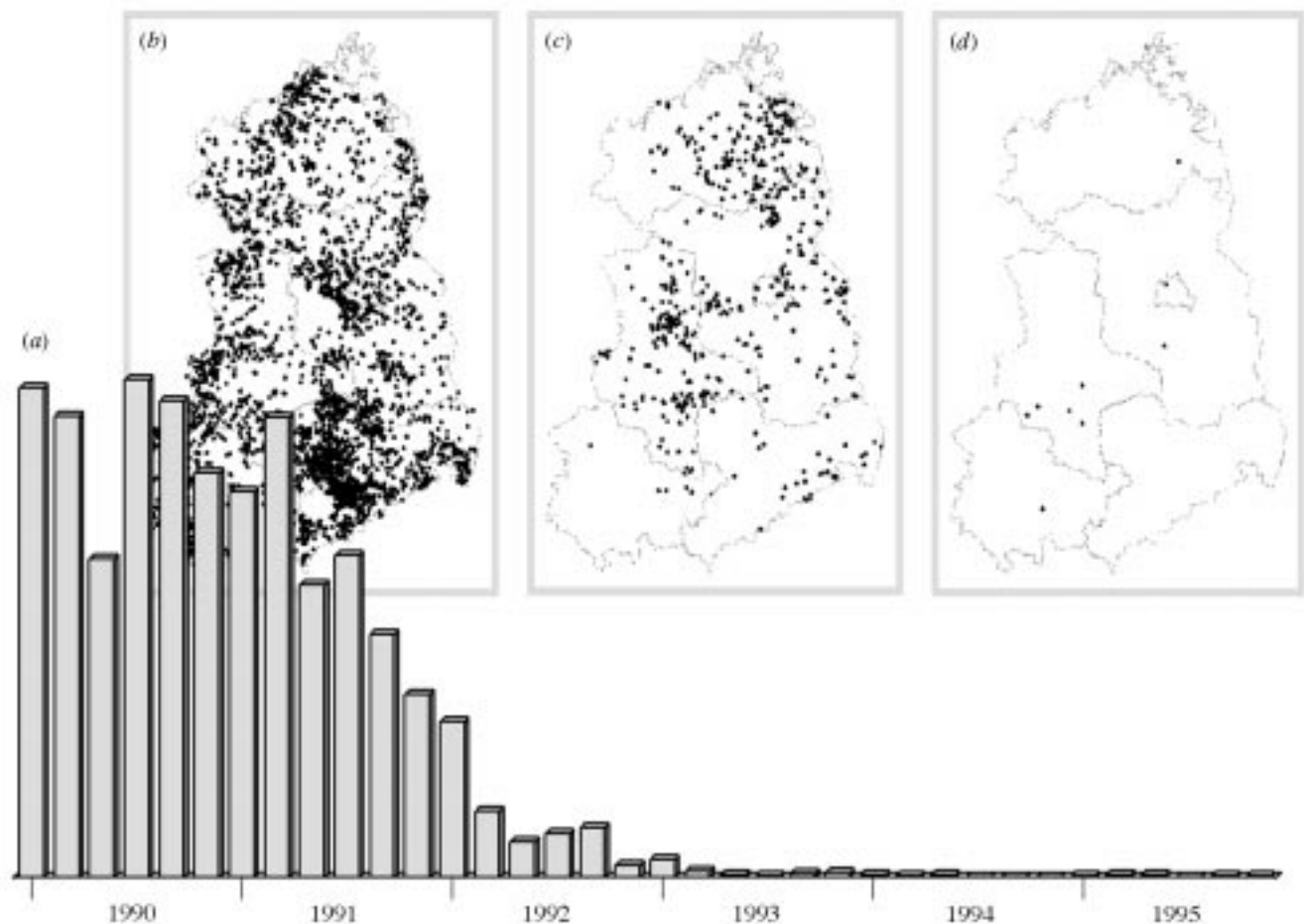


Figure 1. (a) Recorded incidences of rabies in eastern Germany. One of the proofs (black dots) is estimated to indicate between 10 and 50 actual rabid foxes (see text). There is a strong decline in detected rabies prevalence within the first two years after starting the area-wide vaccination in 1990, followed by lasting sporadic incidences. (b–d) The spatial distribution of detected rabies incidences in eastern Germany in 1990 (b), 1992 (c) and 1994 (d).

number of campaigns, over which both eradication and persistence are likely to occur?

2. THE MODEL

To answer the questions posed we adjusted a simulation model (Jeltsch *et al.* 1997), which has originally been developed to investigate the way and cyclic pattern formation of rabies epidemics (Preston 1973; Toma & Andral 1977; Steck & Wandeler 1980; Källén *et al.* 1985; Sayers *et al.* 1985; Murray *et al.* 1986; Curk 1991). In the current version of the model we added a new algorithm to describe the effects of large-scale and long-term vaccination of foxes. In addition, increased fox contact rates during the mating period were included as well as the latest empirical reports about the dispersal of young foxes in eastern Germany, which were used to refine the calibration of dispersal distances (see below). Both mating period and modified dispersal distances did not qualitatively change the spatio-temporal dynamics of the fox rabies systems as compared with the earlier model (Jeltsch *et al.* 1997). However, the additional detail provided by these model modifications was necessary to

realistically evaluate the effect of vaccination on the fox–rabies system.

Our simulation model is a hybrid combining the spatial version of the standard epidemic model based on a two-dimensional grid (Mollison & Kuulasmaa 1985; Durett 1995) with an individual-based approach for longer-range movements (DeAngelis & Gross 1992). It has been designed to describe a single-vector spreading disease in a host population consisting of spatially separated social groups, referred to here as ‘infection communities’ (IFCs). The concept of IFCs is based on the course of sylvatic rabies and on social fox communities in which intragroup contact rates are assumed high enough to spread an infection throughout the whole group within at least two months (for estimates of group contacts see, for example, MacDonald *et al.* (1981), White & Harris (1994) and White *et al.* (1995)). IFCs become spatially arranged by assigning them to cells of the grid (e.g. Hogeweg 1988; Jeltsch *et al.* 1997). Each cell can hold one out of six possible states (see figure 2) covering the potential fate of an IFC. Transitions between these states are probabilistic and depend on the former state of an IFC as well as on its spatial context expressed by three spreading mechanisms

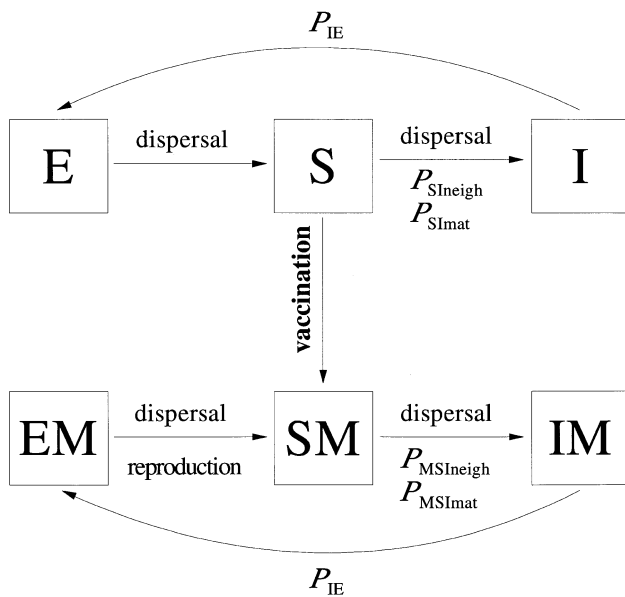


Figure 2. The potential fate of an IFC is covered by three ‘simple’ states, infectious (I), empty (E) and susceptible (S), and, owing to proportional immunization, by three mixed states, susceptible + immune (SM), infectious + immune (IM) and empty + immune (EM) (EM means that only immune foxes are present). In addition to the described transition probabilities (see text and table 1), reproduction refers to the loss of cubs’ immunity and causes a state transition toward SM.

(neighbourhood, mating and dispersal) and the control efficacy (vaccination).

(a) Neighbourhood

The most local spread of rabies is caused by assuming continuous interactions between adjacent IFCs. The probability of infecting a susceptible IFC within two months, P_{neigh} , is calculated from the number (k) of infected neighbouring IFCs (adjacent and diagonal) and the model parameter P_{SIneigh} (see table 1),

$$P_{\text{neigh}} = 1 - (1 - P_{\text{SIneigh}})^k. \quad (1)$$

‘Neighbourhood’ is scheduled at each time step except for mating.

(b) Mating

During the mating period, males may be attracted by calling females from distances up to three home ranges away (J. Goretzki, unpublished data). Consequently we extend the neighbourhood responsible for infecting a susceptible IFC to its three surrounding rings with a step-wise reduced effective probability of infection. The overall infection probability during mating P_{mat} is thus calculated as

$$P_{\text{mat}} = 1 - \{[1 - (P_{\text{SImat}})]^k [1 - (P_{\text{SImat}})^2]^m [1 - (P_{\text{SImat}})^3]^n\}, \quad (2)$$

where P_{SImat} is a model parameter (see table 1). The values k , m and n represent the numbers of infected IFCs within the first (analogue to equation (1)), the second (out of 16 cells) and the third (out of 24 cells) ring of neighbours.

Table 1. The parameters of the model listed with their symbol, their description, the allowed range and the simulation step width

(A total of 1584 configurations (144 for 11 immunization rates) have been simulated. Under immunization, IR reduces P_{SIneigh} and P_{SImat} according to equation (3) (see text).)

| parameter | meaning | range [step width] |
|----------------------|--|-----------------------|
| P_{SIneigh} | transition probability $S \rightarrow \rightarrow \rightarrow I$ by one adjacent IFC within one time step | 0.24–0.4 [0.02] |
| P_{SImat} | transition probability $S \rightarrow \rightarrow \rightarrow I$ by neighbouring IFCs that are located within the three rings around the susceptible IFC (mating activities) | 0.4–0.5 [0.1] |
| P_{IE} | transition probability $I \rightarrow \rightarrow \rightarrow E$ within one time step (mortality caused by rabies) | 0.65–0.8 [0.05] |
| disp | number of dispersing cubs leaving the birth IFC in autumn | 3–4 [1] |
| IR | immunization rate in per cent | 60–80 [2] |

(c) Dispersal

The most remote spread of rabies is caused by the annual dispersal of fox cubs in autumn. We use an individual-based model to describe this spreading mechanism because (i) each single cub may carry the disease to a different location and set up a remote centre of infection, and (ii) movement pattern (Jensen 1973; Storm *et al.* 1976; Trehwella *et al.* 1988) and movement distances (Harris & Trehwella 1988; Allen & Sergeant 1993; Goretzki *et al.* 1997) of dispersing foxes are well documented. Out of ‘disp’ numbers of cubs (see table 1), each cub starts in a random direction and continues in it with a probability of 50%. It may turn right or left with a probability of 25%, respectively (for details, see Jeltsch *et al.* (1997)). After covering a certain distance, which is randomly drawn from a distance distribution obtained by mark–recapture experiments (exponential shape, maximum distance 31 km (Goretzki *et al.* 1997)), the individual stops and settles down. If the IFC of origin is infected, the status of infection is transmitted to the cell of settlement by the disperser. Dispersing cubs that are not infected may recolonize empty cells.

(d) Vaccination

Vaccination immunizes a portion of all susceptible foxes (immunization rate) and reduces crucial contact rates between infected and susceptible foxes. We introduced the time event ‘vaccination’, which changes the states of all actual susceptible IFCs into a partly immunized one (see figure 2). Vaccination is scheduled in spring and autumn according to the conducted control programme. We furthermore added the global parameter IR (see table 1), which determines the reduced contribution of a ‘partly immunized’ IFC to the overall infection probability. The probabilities are calculated by equations (1) and (2), merely using the infection parameter under immunization, P_{Mx} (i.e. P_{MSIneigh} , P_{MSImat}), as

$$P_{\text{Mx}} = P_{\text{x}}(1 - \text{IR}/100), \quad (3)$$

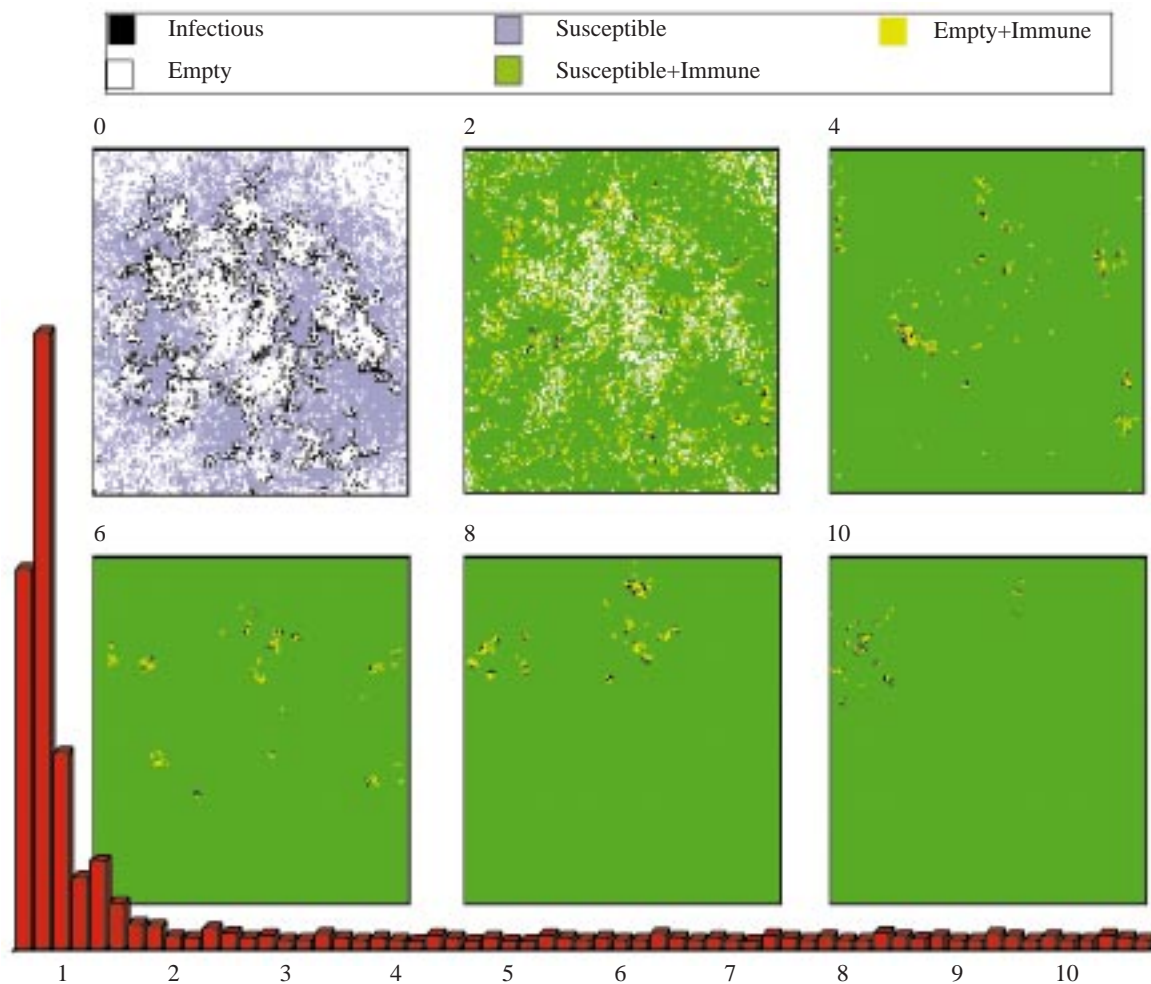


Figure 3. The simulation over ten years of repeated semi-annual vaccination, depicting the definition and the spatial aspect of low-level persistence of rabies (see text). The time series shows the overall prevalence measured after each time step (two months). After the first vaccination at the second time step (spring of year 1), rabies decreases strongly within the following two years. From this point on the actual level of prevalence neither recovers above a fixed limit (0.2% by definition, see text) nor reaches zero. Rabies persists for eight years at a low-level of prevalence. The spatial snapshots plot the initial setting (0, see text) and consecutively every twelfth time step (i.e. year 2, 4, 6, 8 and 10). Resolving the time series biennially in space, the snapshots explain the spatial aspect of the phenomenon: low-level persistence is linked to small, spatio-temporal, moving clusters of infection. Parameter values for this example are: $P_{\text{SIneigh}}=0.34$; $P_{\text{SImat}}=0.4$; $P_{\text{IE}}=0.8$; $\text{disp}=3$; $\text{IR}=70\%$.

instead of the corresponding model parameter without immunization, P_x (i.e. P_{SIneigh} , P_{SImat} ; see table 1). IR is the actual value of the immunization rate, which is kept constant within the population.

The spatial context of our simulations is an open square grid of 19 600 cells with an initial setting of the disease reflecting the state of the epidemic after passing three cyclic maxima (see Jeltsch *et al.* 1997; figure 3, year 0). The grid is updated synchronously at a temporal scale of two months (Jeltsch *et al.* 1997). Each simulation comprises 60 time steps, which corresponds to ten years real time.

We conducted simulations using the standard factorial experimental design (for a similar approach compare Spear & Hornberger (1983) and Fahrig (1991)) by taking values for each parameter out of a meaningful range (see table 1). The parameter ranges were partly predetermined by sensitivity analyses and the pattern oriented verification (Grimm *et al.* 1996) of the original version of this model (Jeltsch *et al.* 1997). Because the sensitivity analysis given in Jeltsch *et al.* (1997) is still

valid for large parts of the current version, we will focus on the sensitivity of model results towards changes of the vaccination intensity. The range of the newly introduced immunization rate has been set between 60% and 80% to cover the empirical observations obtained by surveillance (Steck *et al.* 1982; Schneider *et al.* 1987; Stöhr *et al.* 1994) and by population dynamic models (Anderson *et al.* 1981; Murray & Seward 1992; Schenzle 1995). Despite the large size of the grid, which corresponds to an area of about 20 000–40 000 km², we managed to perform 100 repetitions for each of the resulting 1584 parameter configurations (see table 1) to balance the inherent stochasticity of the model, in particular in view of low-level persisting rabies.

Our results are based on two response measures. First, the occurrence of lasting rabies at a level of prevalence that is hard to detect. In the context of repeated vaccination over many years and for the sake of brevity we call the phenomenon low-level persistence of rabies. The following definition is used to classify our simulations.

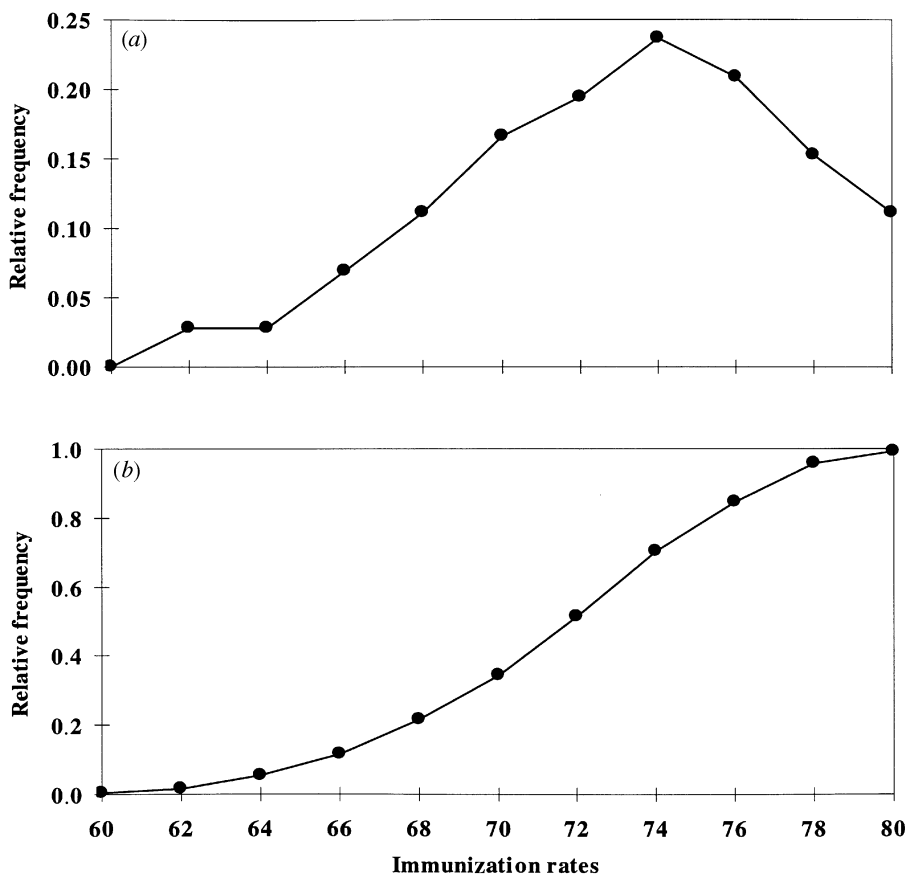


Figure 4. (a) The frequency of low-level persistence of rabies increases up to a maximum at IR = 74% followed by decline. (b) Simultaneously, the frequency of eradication (for calculation, see text) increases steadily with elevating immunization rates. Note that curves (a) and (b) do not add up to 1 because of the non-exclusive selection (see text). A high chance of eradication, such as 97 out of 100 runs (97% eradication), would leave three runs without eradication, which may fit to the definition of 'low-level persistence of rabies'.

The epidemiological set-up in an area of repeated vaccination is said to produce a 'low-level persistence of rabies' if after two initial years the overall prevalence of the disease neither exceeds 0.2% nor becomes zero in that area under control (see figure 3).

For each parameter configuration, representing a particular epidemiological set-up, the occurrence of low-level persistence of rabies was determined by the time series of infected IFCs for 100 repetitions. The value of the upper bound in our definition (0.2%) is motivated by the calibration of the surveillance sample in Germany, which is designed to prove the disease with certainty if the actual prevalence exceeds 0.2%.

Second, for every fixed IR, the relative frequency of eradication (RFE) is determined by the related 144 parameter configurations (see table 1). This measure for eradication is assigned by: (i) calculating the frequency of eradication (FE) out of the 100 repetitions for each single parameter configuration, and (ii) dividing the sum over all FEs by the number of related parameter configurations.

3. RESULTS

(a) Low-level persistence

The simulation results indicate that low-level persistence of the disease (as shown in figure 3) can occur for all investigated immunization rates (60–80%). The spatial patterns associated with low-level persistence are characterized by spatio-temporal moving clusters of infected IFCs (figure 3). This typical spatio-temporal pattern supports the hypothesis that the sporadic inci-

dences (figure 1) are caused by lasting infection seats rather than by immigrating infected foxes from non-immunized regions.

The relationship between the frequency of low-level persistence and the corresponding immunization rate leads to a second important discovery. The frequency of time series expressing low-level persistence increases up to immunization rates of 74% (figure 4a). At higher immunization rates the frequency declines. Although the maximum at 74% may be a consequence of the finite simulation time (ten years), the result clearly shows a general trend: a highly suppressed but incompletely eradicated disease tends to persist at a very low level with an increasing chance at higher suppression unless eradication becomes very likely.

(b) Eradication

The relative frequency of eradication (RFE) increases steadily with increasing immunization rates (see figure 4b). It is noteworthy that the whole range of RFE between almost no chance and a very certain eradication is covered by the chosen range of immunization rates. This agreement with other findings (Anderson *et al.* 1981; Voigt *et al.* 1985; Reichert 1989) further increases the confidence in our model.

The second controlling variable beside the immunization rate is the duration of the vaccination programme or the number of campaigns. We focus attention on a central parameter subspace to obtain a more detailed idea about how RFE might change over time. Even under optimistic circumstances (figure 5, low neighbourhood infection probability $P_{\text{SIneigh}}=0.24$), RFE does not significantly

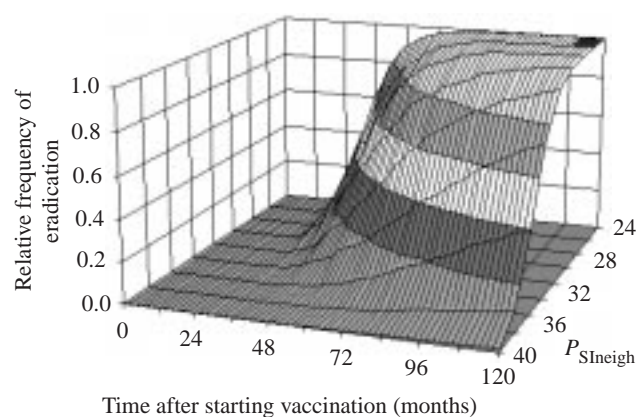


Figure 5. A repeated vaccination for six years may eradicate rabies in some epidemiological settings, as expressed by certain parameter configurations. As shown for a central parameter subspace ($IR = 70\%$), the duration of vaccination is linked to a threshold in the chance of eradication. Up until three years of vaccination, the chance of rabies eradication is small. This is followed by a threshold after which the chance of eradication may increase markedly. However, an accurate risk assessment of the likely success of a certain duration of vaccination in an area requires accurate quantitative knowledge of the respective epidemiological background (i.e. the value of $P_{SIneigh}$).

increase until three years after starting vaccination. There may be a very strong increase of RFE at a threshold between three and six years of repeated vaccination and RFE might become almost unity after six years. However, figure 5 also indicates that the considered variability in the fox–rabies system may cause a wide spectrum of eradication probabilities over time. Detailed quantitative knowledge about the spreading mechanisms in a given area is necessary to make an accurate risk assessment for the region.

4. DISCUSSION

The simulation experiments indicate that the immunized fox–rabies system as surveyed in eastern Germany has the potential to produce a low-level rabies persistence associated with spatio-temporal moving infection clusters. This inherent, typical spatial pattern impedes the detection of potential endemic cases with practicable surveillance measures. Even at detected immunization rates of about 70% and after five years of repeated vaccination, certain eradication cannot be taken for granted. The considered termination of the current vaccination programme therefore leaves a clear residual risk.

The immediate question is how this residual risk can be dealt with in the near future. As our results suggest, risk minimization could clearly be achieved in theory by intensifying the current strategy for a few more years to increase the immunization rate towards 80%. However, continuation of the extensive vaccination strategy decreases the cost–benefit further (Selhorst & Schlüter 1997) and is therefore not recommended. The alternative should involve an immediate post-immunization risk assessment, in particular the examination of the spatio-temporal dynamics of potential new outbreaks and the establishment of a corresponding emergency programme

to deal rapidly and efficiently with potential new local outbreaks.

The model presented is a suitable complement to the vaccination programme, which can be regarded as a large-scale experiment itself. However, this experiment covers a presumably high variability in the fox–rabies system (e.g. diverse population densities and varying immunization rates). Using the standard factorial experimental design (Fahrig 1991) is a suitable way to deal with this high variability and the variety of environmental settings. The empirical knowledge about the particular fox–rabies system provides clues (e.g. average immunization rates and rabies incidences after and during vaccination), but is not yet a basis to provide a quantitative risk assessment. Our simulation study fills this gap to a certain extent and provides quantitative relationships as well as a qualitative estimate about the associated spatial patterns. The demonstrated realism of our model (Barlow 1995), and the harmony with results of models based on completely different approaches (see Pech & Hone 1992; Barlow 1995), additionally strengthens our confidence in the presented results.

Our specific disease-related viewpoint on the fox–rabies system leads to a suitable level of aggregation allowing spatially explicit simulations on a large spatial scale (Jeltsch *et al.* 1997). The chosen combination of a grid-based and individual-based approach thus combines the advantages of more mathematical models explaining epidemiological dynamics on larger scales (e.g. Anderson *et al.* 1981; Bacon 1985; Ball 1985; Smith 1985; Garnerin *et al.* 1986; Murray *et al.* 1986; Schenzle 1995), and strictly individual-based models facilitating an improved understanding of local infection dynamics (e.g. David *et al.* 1982; Voigt *et al.* 1985; Reichert 1989; Smith & Harris 1991; Smith 1995). The combined approach allows for the inclusion of additional aspects of the behaviour of foxes, which may play an important role in the persistence of the disease foci in nature.

We used a homogeneous spatial context as a starting point to keep the model and its understanding as simple as possible. Nevertheless, we are aware of the lack of spatial heterogeneity in terms of landscape configuration and composition, as well as varying immunization rates. Spatial heterogeneity and an examination of the spatio-temporal dynamics of a potential post-vaccination outbreak are both subjects for further research.

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REFERENCES

- Allen, S. H. & Sergeant, A. B. 1993 Dispersal patterns of red foxes relative to population density. *J. Wildl. Mgmt* **57**, 526–533.
- Anderson, R. M., Jackson, H. C., May, R. M. & Smith, A. M. 1981 Population dynamics of fox rabies in Europe. *Nature* **289**, 765–771.
- Bacon, P. J. 1981 The consequences of unreported fox rabies. *J. Envir. Mgmt* **13**, 195–200.
- Bacon, P. J. 1985 Discrete time temporal models of rabies. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 147–195. London: Academic Press.

- Bacon, P. J. & MacDonald, D. W. (eds) 1981 *Habitat classification, fox population and rabies spread*. Merlewood Research and Development Paper 81.
- Ball, F. G. 1985 Spatial models for the spread and control of rabies incorporating group size. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 197–222. London: Academic Press.
- Barlow, N. D. 1995 Critical evaluation of wildlife disease models. In *Ecology of infectious diseases in natural populations* (ed. B. T. Grenfell & A. P. Dobson), pp. 230–259. Cambridge University Press.
- Braunschweig, A. 1980 Ein Modell für die Fuchspopulationsdynamik in der Bundesrepublik Deutschland. In *The red fox, behaviour and ecology* (ed. E. Zimen), pp. 97–106. The Hague: Dr W. Junk.
- Curk, A. 1991 Seasonal and cyclic patterns of fox rabies in Slovenia. *Vet. Archiv* **61**, 19–24.
- David, J. M., Andral, L. & Artois, M. 1982 Computer simulation model of the epi-enzootic disease of vulpine rabies. *Ecol. Model.* **15**, 107–125.
- DeAngelis, D. L. & Gross, L. J. 1992 (eds) *Individual-based models and approaches in ecology: populations, communities and ecosystems*. New York: Chapman & Hall.
- Durrett, R. 1995 Spatial epidemic models. In *Epidemic models—their structure and relation to data* (ed. D. Mollison), pp. 187–201. Cambridge University Press.
- Fahrig, L. 1991 Simulation methods for developing general landscape-level hypotheses of single species dynamics. In *Quantitative methods in landscape ecology* (ed. M. G. Turner & R. H. Gardner), pp. 417–442. Berlin: Springer.
- Garnerin, P., Hazout, S. & Valleron, A.-J. 1986 Estimation of two epidemiological parameters of fox rabies: the length of incubation period and the dispersion distance of cubs. *Ecol. Model.* **33**, 123–135.
- Goretzki, J. & Paustian, K. H. 1982 Zur Biologie des Rotfuchses *Vulpes vulpes* (L., 1758) in einem intensiv landwirtschaftlich genutzten Gebiet. *Beiträge zur Jagd & Wildforschung* **12**, 96–107.
- Goretzki, J., Ahrens, M., Stubbe, C., Töttewitz, F., Sparing, H. & Gleich, E. 1997 Zur Ökologie des Rotfuchses (*Vulpes vulpes* L., 1758) auf der Insel Rügen: Ergebnisse des Jungfuchsfanges und der Jungfuchsmarkierung. *Beiträge zur Jagd & Wildforschung* **22**, 187–199.
- Grimm, V., Frank, K., Jeltsch, F., Brandl, R., Uchmanski, J. & Wissel, C. 1996 Pattern-oriented modelling in population ecology. *Sci. Total Envir.* **183**, 151–166.
- Harris, S. & Trewheella, W. J. 1988 An analysis of some of the factors affecting dispersal in an urban fox (*Vulpes vulpes*) population. *J. Appl. Ecol.* **25**, 409–422.
- Hogeweg, P. 1988 Cellular automata as a paradigm for ecological modelling. *Appl. Math. Comput.* **27**, 81–100.
- Jeltsch, F., Müller, M. S., Grimm, V., Wissel, C. & Brandl, R. 1997 Pattern formation triggered by rare events: lessons from the spread of rabies. *Proc. R. Soc. Lond. B* **264**, 495–503.
- Jensen, B. 1973 Movements of the red fox (*Vulpes vulpes*) in Denmark investigated by marking and recovery. *Dan. Rev. Game Biol.* **8**, 3–20.
- Källén, A., Arcuri, P. & Murray, J. D. 1985 A simple model for spatial spread and control of rabies. *J. Theor. Biol.* **116**, 377–393.
- Macdonald, D. W., Bunce, R. G. H. & Bacon, P. J. 1981 Fox populations, habitat characterization and rabies control. *J. Biogeogr.* **8**, 145–151.
- Masson, E., Aubert, M. F. A., Barrat, J. & Vuillaume, P. 1996 Comparison of the efficacy of the antirabies vaccines used for foxes in France. *Vet. Res.* **27**, 255–266.
- Meslin, F. M. 1997 Zoonoses in the world: current and future trends. In *Information circular*. WHO Mediterranean Zoonoses Control Centre **42**, 2–4.
- Mollison, D. & Kuulasmaa, K. 1985 Spatial epidemic models: theory and simulations. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 291–309. London: Academic Press.
- Murray, J. D. & Seward, W. L. 1992 On the spatial spread of rabies among foxes with immunity. *J. Theor. Biol.* **156**, 327–348.
- Murray, J. D., Stanley, E. A. & Brown, D. L. 1986 On the spatial spread of fox rabies among foxes. *Proc. R. Soc. Lond. B* **229**, 111–150.
- Pech, R. P. & Hone, J. 1992 Models of wildlife rabies. In *Wildlife rabies contingency planning in Australia* (ed. P. O. Brian & G. Berry), pp. 147–156. Canberra: Australian Government Publishing Service.
- Preston, E. M. 1973 Computer simulated dynamics of a rabies-controlled fox population. *J. Wildl. Mgmt* **37**, 501–512.
- Reichert, H.-U. 1989 Simulationsstudien zur Ausbreitung und Bekämpfung der Tollwut bei Füchsen mit einem stochastischen, räumlichen Modell. PhD thesis, University of Tübingen, Germany.
- Rupprecht, C. E., Dietzschold, B. & Koprowski, H. 1994 *Lyssaviruses*. Heidelberg: Springer.
- Sayers, B. M., Ross, J. A., Saengcharoenrat, P. & Mansourian, B. G. 1985 Pattern analysis of case occurrence of fox rabies in Europe. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 235–254. London: Academic Press.
- Schenzle, D. 1995 Zur Frage der weiteren Tollwutbekämpfung in Deutschland. *Deutsche Tierärztliche Wochenschrift* **102**, 421–424.
- Schlüter, H. & Müller, T. 1995 Tollwutbekämpfung in Deutschland. Ergebnisse und Schlußfolgerungen aus über 10-jähriger Bekämpfung. *Tierärztl. Umschau* **50**, 748–758.
- Schneider, L. G., Cox, J. H. & Müller, W. W. 1987 Ein Feldversuch zur oralen Immunisierung von Füchsen gegen die Tollwut in der Bundesrepublik Deutschland. Unschädlichkeit, Wirksamkeit und Stabilität der Vaccine SAD B19. *Tierärztl. Umschau* **38**, 315–324.
- Selhorst, T. & Schlüter, H. 1997 Cost-benefit analysis of the oral immunisation strategy for the control of rabies in fox populations. *Epidemiol. sante anim.* **31–32**, 10.20.1–10.20.3.
- Smith, A. D. M. 1985 A continuous time deterministic model of temporal rabies. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 131–146. London: Academic Press.
- Smith, G. C. 1995 Modelling rabies control in the UK: the inclusion of vaccination. *Mammalia* **59**, 629–637.
- Smith, G. C. & Harris, S. 1991 Rabies in urban foxes (*Vulpes vulpes*) in Britain: the use of a spatial stochastic simulation model to examine the pattern of spread and evaluate the efficiency of different control regimes. *Phil. Trans. R. Soc. Lond. B* **334**, 459–479.
- Spear, R. C. & Hornberger, G. M. 1983 Control of OO level in river under uncertainty. *Water Resource Res.* **19**, 126–1270.
- Steck, F. & Wandeler, A. 1980 The epidemiology of fox rabies in Europe. *Epidemiol. Rev.* **2**, 71–96.
- Steck, F., Wandeler, A., Bichsel, P., Capt, S. & Schneider, L. G. 1982 Oral immunisation of foxes against rabies. *Zbl. Vet. Med. B* **29**, 372–396.
- Stöhr, K. & Meslin, F.-M. 1996 Progress and setbacks in the oral immunisation of foxes against rabies in Europe. *Vet. Rec.* **139**, 32–35.
- Stöhr, K., Stöhr, P. & Müller, T. 1994 Orale Fuchsimpfung gegen Tollwut—Ergebnisse und Erfahrungen aus den ostdeutschen Bundesländern. *Tierärztl. Umschau* **49**, 203–211.
- Storm, G. L., Andrews, R. D., Phillips, R. L., Bishop, R. A., Siniff, D. B. & Tester, J. R. 1976 Morphology, reproduction, dispersal, and mortality of midwestern red fox populations. *Wildl. Monogr.* **49**, 1–82.
- Toma, B. & Andral, L. 1977 Epidemiology of fox rabies. *Adv. Virus Res.* **21**, 1–36.

- Trehwella, W. J., Harris, S. & McAllister, F. E. 1988 Dispersal distance, home range size and population density in the red fox (*Vulpes vulpes*): a qualitative analysis. *J. Appl. Ecol.* **25**, 423–434.
- Voigt, D. R., Tinline, R. R. & Broekhoven, L. H. 1985 A spatial simulation model for rabies control. In *Population dynamics of rabies in wildlife* (ed. P. J. Bacon), pp. 311–349. London: Academic Press.
- White, P. L. & Harris, S. 1994 Encounters between red foxes (*Vulpes vulpes*): implications for territory maintenance, social cohesion and dispersal. *J. Anim. Ecol.* **63**, 315–327.
- White, P. L., Harris, S. & Smith, G. C. 1995 Fox contact behaviour and rabies spread: a model for the estimation of contact probabilities between urban foxes at different population densities and its implications for rabies control in Britain. *J. Appl. Ecol.* **32**, 693–706.
- WHO 1990a *Rabies bulletin Europe*. Collaborating Centre for Rabies Surveillance and Research, Tübingen, Germany, 4th quarter 1990, 11.
- WHO 1990b *Report of the seminar on wildlife rabies control*. WHO/CDS/PH/90.93, Geneva, 2–5 July.